Application of DoD Biodetector Technology to Coupled Detection and Intervention in Precancerous Patients and to Health Maintenance in Space

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Summary:
The ability to rapidly detect extremely small quantities of molecular-level targets has been demonstrated in microfluidic systems developed under DoD funding for the detection of bio/chemical warfare agents. Integrated DNA assays including sample acquisition, preparation, analysis and detection have been demonstrated. Unique, biomimetic, functional assay screening methods for toxins based on *in vitro* reconstitution of their *in vivo* activity have also been demonstrated. We will describe how the advances demonstrated in the biodetector program can be extended and adapted to a new class of implantable, ingestible or injectable systems: (1) to couple the detection of precancerous biomarkers with the targeted delivery of customized therapeutic interventions, and (2) to maintain health on extended space voyages.

Abstract:
To eliminate the threat of cancer and to maintain health on long space voyages requires tools to detect and destroy, or to detect and reverse the course of disease in healthy, asymptomatic patients. To be routinely used and accepted, these tools must operate in a screening mode; which means they must be simple, painless and inexpensive enough to be used pervasively and frequently, yet sensitive and specific enough to find and recognize biomolecular signatures that may be present in the body at extremely low concentrations. This challenge is, in many ways, similar to the DoD challenge of biowarfare agent detection, in which extremely low absolute numbers of pathogens must be found either in the air or in the body. Both applications require extremely high sensitivity (capability to find extremely low levels of target) and specificity (low false positive detection and essentially zero false negative detection). For both applications, detection of a single molecular-level target is rarely sufficient; detection of targets that are both spatially and temporally heterogeneous is needed to obtain a signature that can be used to reliably direct subsequent action.

In the biowarfare detection community, collection and concentration of the target from a background full of interferents is acknowledged as a critical element of the overall challenge. Biowarfare detection systems begin with a front-end stage that samples and concentrates the target for analysis. To achieve this sample collection and concentration function with in vivo targets, implantable or ingestible microsystems will ultimately be required to reach desired sensitivity levels. Routine sample and test of blood and other body fluids will not suffice, because of the low probability that target biomarkers will be present in any given sample to allow detection of their presence. Microexplorers capable of in-body detection and exploration are also critical to achieve the vision of coupled detection and intervention that is required for truly non-intrusive health maintenance. While external electronic control of implanted/ingested devices has been demonstrated (via techniques such as RF telemetry), microexplorers will ultimately need to function autonomously in order to be non-intrusive.

To this end, Sarnoff has demonstrated fully autonomous microfluidic systems to detect extremely small quantities of molecular-level targets. This work has been funded by DARPA for the detection of bio/chemical warfare agents. Key integrated on-chip advances include: high yield sample collection and preconcentration to isolate targets from a noisy fluidic background; cell lysis; isolation of DNA from cellular debris; simultaneous multiplex amplification of target DNA sequences; and high-throughput, multiplexed and parallel hybridization/read-out. In addition unique functional assay screening methods for toxins based on *in vitro* reconstitution of their *in vivo* activity have been demonstrated. These biomimetic functional assays show tremendous potential for multifunctional systems based on intracellular signal transduction pathways.

We will describe how the advances demonstrated in the biodetector program can be extended and adapted to a new class of implantable, ingestible or injectable systems: (1) to couple the detection of precancerous biomarkers with the targeted delivery of customized therapeutic interventions, and (2) to maintain health on extended space voyages. While program work to-date has focused primarily on developing high-sensitivity microscale assays on the integration of sample acquisition, preparation, analysis and detection, our work in microfluidics and in the fabrication of microfabricated systems that integrate hardware and "wetware" can be directly extended and adapted to achieve targeted delivery of customized therapeutic interventions. We are in the process of forming strategic partnerships in this new area, and welcome the opportunity presented by the NASA/NCI workshop.